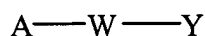


**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings of claims in the application:

**Listing of Claims:**

1                   1 (previously presented): A nucleic acid-lipid particle composition for  
2 introducing a nucleic acid into a cell, said particle composition comprising:  
3                   (a) a nucleic acid-lipid particle comprising a cationic lipid, a conjugated lipid that  
4 inhibits aggregation of particles, and a nucleic acid, wherein said nucleic acid is encapsulated in  
5 AZa lipid bilayer of said nucleic acid-lipid particle, and wherein said conjugated lipid that  
6 inhibits aggregation of particles is a member selected from the group consisting of a PEG-lipid,  
7 an ATTA-lipid and a cationic-polymer-lipid conjugate having the formula



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8  
9 wherein:

10                   A is a lipid moiety;

11                   W is a hydrophilic polymer; and

12                   Y is a polycationic moiety; and

13                   (b) an endosomal membrane destabilizer, wherein said endosomal membrane  
14 destabilizer is  $Ca^{++}$  ion.

1                   2 (original): The nucleic acid-lipid particle composition of claim 1, wherein said  
2 endosomal membrane destabilizer is outside said nucleic acid-lipid particle.

1                   3 (original) The nucleic acid-lipid particle composition of claim 1, wherein said  
2 endosomal membrane destabilizer is both outside and inside said nucleic acid-lipid particle.

4 (cancelled)

1                   5 (original): The nucleic acid-lipid particle composition of claim 4, wherein the  
2 concentration of  $\text{Ca}^{++}$  ion is from about 0.1 mM to about 100 mM.

1                   6 (original): The nucleic acid-lipid particle composition of claim 5, wherein the  
2 concentration of  $\text{Ca}^{++}$  ion is from about 1 mM to about 20 mM.

1                   7 (original): The nucleic acid-lipid particle composition of claim 1, wherein said  
2 particle has a median diameter of less than about 150 nm.

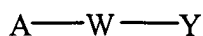
1                   8 (original): The nucleic acid-lipid particle composition of claim 1, wherein said  
2 cationic lipid is a member selected from the group consisting of N,N-dioleoyl-N,N-  
3 dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide  
4 (DDAB), N-(1-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTAP), N-(1-  
5 (2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), and N,N-dimethyl-2,3-  
6 dioleoyloxy)propylamine (DODMA), and combinations thereof.

1                   9 (original): The nucleic acid-lipid particle composition of claim 1, wherein said  
2 particle further comprises an additional noncationic lipid.

1                   10 (original): The nucleic acid-lipid particle composition of claim 9, wherein  
2 said noncationic lipid is selected from the group consisting of DOPE, POPC, and EPC.

1                   11 (original): The nucleic acid-lipid particle composition of claim 1, wherein  
2 said particle comprises a functional group that facilitates  $\text{Ca}^{++}$  ion chelation.

1                   12 (original): The nucleic acid-lipid particle composition of claim 1, wherein  
2 said conjugated lipid that inhibits aggregation of particles has the formula



I

3  
4 wherein:

5           A is a lipid moiety;  
6           W is a hydrophilic polymer; and  
7           Y is a polycationic moiety.

1           13 (original): The nucleic acid-lipid particle composition of claim 12, wherein W  
2 is a polymer selected from the group consisting of PEG, polyamide, polylactic acid, polyglycolic  
3 acid, polylactic acid/polyglycolic acid copolymers and combinations thereof, said polymer  
4 having a molecular weight of about 250 to about 7000 daltons.

1           14 (original): The nucleic acid-lipid particle composition of claim 12, wherein Y  
2 has at least 4 positive charges at a selected pH.

1           15 (original): The nucleic acid-lipid particle composition of claim 12, wherein Y  
2 is a member selected from the group consisting of lysine, arginine, asparagine, glutamine,  
3 derivatives thereof and combinations thereof.

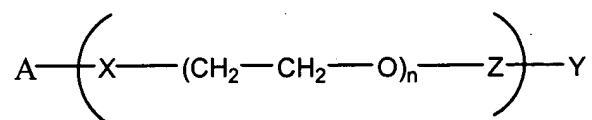
1           16 (original): The nucleic acid-lipid particle composition of claim 12, wherein A  
2 is a member selected from the group consisting of a diacylglycerol moiety, a dialkylglycerol  
3 moiety, a N-N-dialkylamino moiety, a 1,2-diacyloxy-3-aminopropane moiety and a 1,2-dialkyl-  
4 3-aminopropane moiety.

1           17 (original): The nucleic acid-lipid particle composition of claim 12, wherein W  
2 is PEG.

1           18 (original): The nucleic acid-lipid particle composition of claim 12, wherein W  
2 is a polyamide polymer.

1           19 (original): The nucleic acid-lipid particle composition of claim 12, wherein W  
2 has a molecular weight of about 250 to about 2000 daltons.

20 (original): The nucleic acid-lipid particle composition of claim 17, having the general structure of Formula II:



**II**

wherein

X is a member selected from the group consisting of a single bond or a functional group covalently attaching said lipid to at least one ethylene oxide unit;

Z is a member selected from the group consisting of a single bond or a functional group covalently attaching said at least one ethylene oxide unit to a cationic group; and

n is an integer having a value of between about 6 to about 50.

21 (original): The nucleic acid-lipid particle composition of claim 20, wherein

X is a member selected from the group consisting of a single bond, phosphatidylethanolamino, phosphatidylethanolamido, phosphoro, phospho, phosphoethanolamino, phosphoethanolamido, carbonyl, carbamate, carboxyl, carbonate, amido, thioamido, oxygen, sulfur and NR, wherein R is a hydrogen or alkyl group.

22 (original): The nucleic acid-lipid particle composition of claim 20, wherein

Z is a member selected from the group consisting of a single bond, phosphatidylethanolamino, phosphatidylethanolamido, phosphoro, phospho, phosphoethanolamino, phosphoethanolamido, carbonyl, carbamate, carboxyl, carbonate, amido, thioamido, oxygen, sulfur and NR, wherein R is a hydrogen or alkyl group.

23 (original): The nucleic acid-lipid particle composition of claim 20, wherein

A is a diacylglycerol moiety;

X is phosphoethanolamido;

Z is NR, wherein R is a hydrogen atom; and

5           Y is a member selected from the group consisting of about 1 to about 10 basic  
6 amino acids or derivatives thereof.

1           24 (original): The nucleic acid-lipid particle composition of claim 23, wherein  
2           A is a diacylglycerol moiety having 2 fatty acyl chains, wherein each acyl chain  
3 is independently between 2 and 30 carbons in length and is either saturated or has varying  
4 degrees of saturation.

1           25 (original): The nucleic acid-lipid particle composition of claim 23, wherein  
2           Y is a member selected from the group consisting of lysine, arginine, asparagine,  
3 glutamine, derivatives thereof and combinations thereof.

1           26 (original): The nucleic acid-lipid particle composition of claim 23, wherein  
2           A is a diacylglycerol moiety having 2 fatty acyl chains, wherein each acyl chain  
3 is a saturated C-18 carbon chain; and  
4           Y is a cationic group having 4 lysine residues or derivatives thereof.

1           27 (original): The nucleic acid-lipid particle composition of claim 1, wherein  
2 said conjugated lipid that inhibits aggregation of particles is a PEG-lipid

1           28 (original): The nucleic acid-lipid particle composition of claim 27, wherein  
2 said PEG-lipid is PEG-ceramide.

1           29 (original): The nucleic acid-lipid particle composition of claim 28, wherein  
2 the ceramide of said PEG-ceramide comprises a fatty acid group having about 8 to about 20  
3 carbon atoms.

1           30 (original): The nucleic acid-lipid particle composition of claim 28, wherein  
2 said PEG-lipid is PEG-phosphatidylethanolamine.

1                   31 (original): The nucleic acid-lipid particle composition of claim 1, wherein  
2 said conjugated lipid that inhibits aggregation of particles is an ATTA-lipid.

1                   32 (original): The nucleic acid-lipid particle composition of claim 1, wherein  
2 said nucleic acid is selected from the group consisting of a plasmid, an antisense oligonucleotide,  
3 and a ribozyme.

1                   33 (previously presented): A method of introducing a nucleic acid into a cell,  
2 said method comprising:

3                   contacting said cell with a nucleic acid-lipid particle composition, said particle  
4 composition comprising:

5                   (a) a nucleic acid-lipid particle comprising a cationic lipid, a conjugated lipid that  
6 inhibits aggregation of particles, and a nucleic acid, wherein said nucleic acid is encapsulated in  
7 a lipid bilayer of said nucleic acid-lipid particle, and wherein said conjugated lipid that inhibits  
8 aggregation of particles is a member selected from the group consisting of a PEG-lipid, an  
9 ATTA-lipid and a cationic-polymer-lipid conjugate having the formula



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10  
11 wherein:

12                   A is a lipid moiety;

13                   W is a hydrophilic polymer; and

14                   Y is a polycationic moiety; and

15                   (b) an endosomal membrane destabilizer, wherein said endosomal membrane  
16 destabilizer is  $Ca^{++}$  ion.

1                   34 (original): The method of introducing a nucleic acid into a cell of claim 33,  
2 wherein said endosomal membrane destabilizer is outside said nucleic acid-lipid particle.

1                   35 (original): The method of introducing a nucleic acid into a cell of claim 33,  
2 wherein said endosomal membrane destabilizer is  $\text{Ca}^{++}$  ion.

1                   36 (original): The method of introducing a nucleic acid into a cell of claim 35,  
2 wherein the concentration of  $\text{Ca}^{++}$  ion is from about 0.1 mM to about 100 mM.

1                   37 (original): The method of introducing a nucleic acid into a cell of claim 36,  
2 wherein the concentration of  $\text{Ca}^{++}$  ion is from about 1 mM to about 20 mM.

1                   38 (original): The method of introducing a nucleic acid into a cell of claim 33,  
2 wherein said particle has a median diameter of less than about 150 nm.

1                   39 (original): The method of introducing a nucleic acid into a cell of claim 33,  
2 wherein said cationic lipid is a member selected from the group consisting of N,N-dioleoyl-N,N-  
3 dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide  
4 (DDAB), N-(1-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTAP), N-(1-  
5 (2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), and N,N-dimethyl-2,3-  
6 dioleoyloxy)propylamine (DODMA), and combinations thereof.

1                   40 (original): The method of introducing a nucleic acid into a cell of claim 33,  
2 wherein said particle further comprises an additional noncationic lipid.

1                   41 (original): The method of introducing a nucleic acid into a cell of claim 40,  
2 wherein said noncationic lipid is selected from the group consisting of DOPE, POPC, and EPC.

1                   42 (original): The method of introducing a nucleic acid into a cell of claim 33,  
2 wherein said particle comprises a functional group that facilitates  $\text{Ca}^{++}$  ion chelation.

1                   43 (original): The method of introducing a nucleic acid into a cell of claim 33,  
2 wherein said conjugated lipid that inhibits aggregation of particles has the formula



I

wherein:

A is a lipid moiety;

W is a hydrophilic polymer; and

Y is a polycationic moiety.

44 (original): The method of introducing a nucleic acid into a cell of claim 43, wherein W is a polymer selected from the group consisting of PEG, polyamide, polylactic acid, polyglycolic acid, polylactic acid/polyglycolic acid copolymers and combinations thereof, said polymer having a molecular weight of about 250 to about 7000 daltons.

45 (original): The method of introducing a nucleic acid into a cell of claim 43, wherein Y has at least 4 positive charges at a selected pH.

46 (original): The method of introducing a nucleic acid into a cell of claim 43, wherein Y is a member selected from the group consisting of lysine, arginine, asparagine, glutamine, derivatives thereof and combinations thereof.

47 (original): The method of introducing a nucleic acid into a cell of claim 43, wherein A is a member selected from the group consisting of a diacylglycerol moiety, a dialkylglycerol moiety, a N-N-dialkylamino moiety, a 1,2-diacyloxy-3-aminopropane moiety and a 1,2-dialkyl-3-aminopropane moiety.

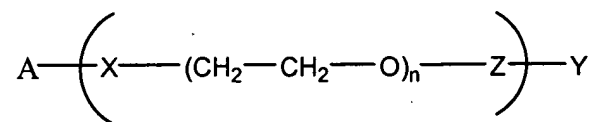
48 (original): The method of introducing a nucleic acid into a cell of claim 43, wherein W is PEG.

49 (original): The method of introducing a nucleic acid into a cell of claim 43, wherein W is a polyamide polymer.



50 (original): The method of introducing a nucleic acid into a cell of claim 43,  
wherein W has a molecular weight of about 250 to about 2000 daltons.

51 (original): The method of introducing a nucleic acid into a cell of claim 48,  
having the general structure of Formula II:



**II**

wherein

X is a member selected from the group consisting of a single bond or a functional  
group covalently attaching said lipid to at least one ethylene oxide unit;

Z is a member selected from the group consisting of a single bond or a functional  
group covalently attaching said at least one ethylene oxide unit to a cationic group; and

n is an integer having a value of between about 6 to about 50.

52 (original): The method of introducing a nucleic acid into a cell of claim 51,  
wherein

X is a member selected from the group consisting of a single bond,  
phosphatidylethanolamino, phosphatidylethanolamido, phosphoro, phospho,  
phosphoethanolamino, phosphoethanolamido, carbonyl, carbamate, carboxyl, carbonate, amido,  
thioamido, oxygen, sulfur and NR, wherein R is a hydrogen or alkyl group.

53 (original): The method of introducing a nucleic acid into a cell of claim 51,  
wherein

Z is a member selected from the group consisting of a single bond,  
phosphatidylethanolamino, phosphatidylethanolamido, phosphoro, phospho,  
phosphoethanolamino, phosphoethanolamido, carbonyl, carbamate, carboxyl, carbonate, amido,  
thioamido, oxygen, sulfur and NR, wherein R is a hydrogen or alkyl group.

1                   54 (original): The method of introducing a nucleic acid into a cell of claim 51,  
2 wherein  
3                   A is a diacylglycerol moiety;  
4                   X is phosphoethanolamido;  
5                   Z is NR, wherein R is a hydrogen atom; and  
6                   Y is a member selected from the group consisting of about 1 to about 10 basic  
7 amino acids or derivatives thereof.

1                   55 (original): The method of introducing a nucleic acid into a cell of claim 54,  
2 wherein  
3                   A is a diacylglycerol moiety having 2 fatty acyl chains, wherein each acyl chain  
4 is independently between 2 and 30 carbons in length and is either saturated or has varying  
5 degrees of saturation.

1                   56 (original): The method of introducing a nucleic acid into a cell of claim 54,  
2 wherein  
3                   Y is a member selected from the group consisting of lysine, arginine, asparagine,  
4 glutamine, derivatives thereof and combinations thereof.

1                   57 (original): The method of introducing a nucleic acid into a cell of claim 54,  
2 wherein  
3                   A is a diacylglycerol moiety having 2 fatty acyl chains, wherein each acyl chain  
4 is a saturated C-18 carbon chain; and  
5                   Y is a cationic group having 4 lysine residues or derivatives thereof.

1                   58 (original): The method of introducing a nucleic acid into a cell of claim 33,  
2 wherein said conjugated lipid that inhibits aggregation of particles is a PEG-lipid.

1                   59 (original): The method of introducing a nucleic acid into a cell of claim 58,  
2 wherein said PEG-lipid is PEG-ceramide.

1                   60 (original): The method of introducing a nucleic acid into a cell of claim 59,  
2 wherein the ceramide of said PEG-ceramide comprises a fatty acid group having about 8 to about  
3 20 carbon atoms.

1                   61 (original): The method of introducing a nucleic acid into a cell of claim 59,  
2 wherein said PEG-lipid is PEG-phosphatidylethanolamine.

1                   62 (original): The method of introducing a nucleic acid into a cell of claim 33,  
2 wherein said conjugated lipid that inhibits aggregation of particles is an ATTA-lipid.

1                   63 (original): The method of introducing a nucleic acid into a cell of claim 33,  
2 wherein said nucleic acid is selected from the group consisting of a plasmid, an antisense  
3 oligonucleotide, and a ribozyme.

64-67 (cancelled)